Thyroid Disorders and Influence of Adjusted Iodine Prophylaxis in Pelagonia and Southwest Regions, North Macedonia

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Abstract

Introduction: Iodine intake influences the incidence of thyroid diseases (TD), but data on its impact after iodine prophylaxis correction remains limited. This study analyzes TD incidence in a part of a country with sufficient iodine status since 2003, covering the period from 1984 to 2021, and evaluates changes following the 1999 iodine prophylaxis correction. **Methods:** This retrospective longitudinal study reviewed 20,880 medical records from a secondary medical center. Demographic and TD data were analyzed descriptively to compare trends before and after the 1999 iodine prophylaxis correction. **Results:** Among 20,880 patients aged 46.63 ± 15.06 years, 18,182 (87.1%) were female. Hypothyroidism (40.43%) and euthyroid nodular goiter (ENG) (28.7%) were predominant TD. Before the iodine prophylaxis correction, the mean patient age was 40.03 ± 13.03 years, with ENG (27.29%), hyperthyroidism (24.78%), euthyroid diffuse goiter (EDG) (24.94%), and hypothyroidism (15.84%) dominating. After the 1999 iodine prophylaxis correction, the overall incidence of TD, mean age (47.54 ± 15.1 years), male representation ($P < 0.001$), and hypothyroidism (43.78%, $P < 0.001$) increased, while EDG (11.73%), hyperthyroidism (12.28%), toxic nodular goiter (1.42%), and thyroid carcinoma (0.16%) declined (overall $P < 0.001$). ENG incidence (28.89%, $P = 0.102$) remained unchanged. **Conclusion:** Hypothyroidism and ENG were the predominant thyroid disorders in the area. Corrected iodine prophylaxis increased overall TD incidence, age at diagnosis, male representation, and hypothyroidism while reducing most other TD incidences. The stable ENG incidence requires further investigation. Continued monitoring is essential to improve public health strategies for TD management.

Keywords: Hypothyroidism, incidence, iodine prophylaxis, thyroid diseases

Introduction

Iodine intake affects thyroid disease (TD) incidence, functionally categorized as hypothyroidism and hyperthyroidism[1,2] and morphologically as diffuse or nodular goiter and thyroid carcinoma (TC).[3,4] Women suffer 5 to 8 times more frequently than men.[5]

Hyperthyroidism affects 0.2%–1.3% of the population, while hypothyroidism ranges from 0.2%–5.3%, mainly in individuals over 65.[6] The prevalence of ultrasound-detected goiter is between 19% to 35%.[4,7] In 2022, TC was the seventh most prevalent cancer worldwide, causing 47,507 deaths, predominantly in Asia.[8]

TD occurrence is affected by genetic variations, gender, age, and iodine intake.[1,3,9] Iodine deficiency increases hypothyroidism and goiter prevalence,[10] while sufficiency raises autoimmune thyroid diseases (AITD).[11] Other contributing factors include selenium and vitamin D deficiency, radiation, chemicals, heavy metals, medications, smoking, viral infections, goitrogenic substances, obesity, and metabolic syndrome.[12-14]

In North Macedonia, iodine fortification of salt began in 1956 with 10 mg of potassium iodide per kilogram (KI/kg), followed by 5-25 mg KI/kg until 1995/1996,[15] with a high rate of diffuse and nodular goiter and hyperthyroidism detected.[16] In

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1999, mandatory iodization was standardized to 20–30 mg of iodine/kg of salt using potassium iodate (KIO_3), eliminating iodine deficiency by 2003.[15] A 2018 evaluation reported average urinary iodine concentrations of 216 μg/L in children and 177 μg/L in pregnant women,[17] indicating adequate to more-than-adequate iodine intake, respectively.[10]

Despite improvements, limited data exist on the effects of iodine fortification.[15] The study aimed to evaluate TD trends in the part of the country from 1984 to 2021 and assess the changes following the 1999 iodine prophylaxis correction.

Materials and Methods

This retrospective longitudinal study analyzed 20,880 records from a regional secondary medical center registered between 1984 and 2021. Thyroid patients originated from Regions 1 and 2. Data was divided into two groups based on the 1999 iodine prophylaxis correction: group 1 (1984–1999) before and group 2 (2000–2021) after the correction. Demographic data originated from the State Statistics Office.[18]

Thyroid function

Thyroid function was assessed by recorded levels of TSH (0.4–4.0 μIU/mL), free thyroxine (fT4) (9.0–24.7 pmol/L), and thyroid peroxidase (TPO) antibodies (<35 mIU/mL). Measurements were performed using radioimmune assay (RIA) until 2003, followed by ELISA and the IMMULITE 1000 (Siemens, Germany) until 2008, and then the IMMULITE 2000 (Siemens, Germany). Patient treatment histories, including usage of levothyroxine for hypothyroidism and antithyroid medications (thiamazole or propylthiouracil) for hyperthyroidism, were documented.

Ultrasound imaging

Thyroid nodule evaluations were performed via unspecified manufacturer ultrasound until 2003, followed by a Toshiba system (Japan) until 2020. Afterward, a 10 MHz linear multifrequency transducer (5-10 MHz, L40) (RAMZED, model RZ-VD6, China) was used. TC was diagnosed via pathohistological analysis following thyroidectomy.

Based on initial thyroid function tests, ultrasound, and pathohistological findings, TDs were classified into eight categories: hypothyroidism (primary, congenital, or post-procedural), euthyroid Hashimoto thyroiditis, hyperthyroidism, toxic nodular goiter (TNG), euthyroid nodular goiter (ENG), euthyroid diffuse goiter (EDG), subacute thyroiditis, and TC.

Statistical analysis

Numerical variables were presented as mean ± standard deviation (SD), with minimum, maximum, median, and mode values. Categorical variables were presented as frequency and percentage values. The incidence of TD was analyzed by gender, age, municipality of origin, and year of registration. Comparisons between groups were conducted using the Student's *t*-test for numerical variables and Pearson's Chi-squared (χ^2) test for categorical variables in independent samples. Box-plot analysis illustrated the age at diagnosis across different TD types, with multiple comparisons performed using the Analysis of Variance (ANOVA) test. The annual TD incidence per 100,000 inhabitants was estimated by dividing the number of new cases by the population of Region 1 in 1994, 2002, and 2021, using census data.[19] Statistical analysis was performed using IBM SPSS Statistics v. 27.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp), with P value < 0.05 considered statistically significant.

Ethical aspects

The study protocol was approved by the Ethics Committee for Human Research at the Faculty of Medicine, University Ss. Cyril and Methodius in Skopje, Republic of North Macedonia (permission number 03-3951/3, dated 27 September 2022). Due to the retrospective nature of the study, patient consent was not required and the Ethics Committee waived the consent. The study was performed by the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments.

Results

The study included 20,880 patients: 18,182 women (87.1%) and 2,698 men (12.9%) aged 0 to 99 years. The overall mean age at diagnosis was 46.63 ± 15.06 years (median 47, mode 54). Women had a mean age of 46.2 ± 14.8 years (median 47, mode 54), while men were, on average, 3.34 years older, with a mean age of 49.55 ± 16.52 years (median 51, mode 52). The difference was statistically significant ($\chi^2 = 11.482$; $P < 0.001$; 95% CI 2.74–3.95).

As shown in Table 1, nearly two-thirds of the patients were diagnosed with hypothyroidism and ENG, followed by hyperthyroidism, EDG, TNG, euthyroid Hashimoto's thyroiditis, and subacute thyroiditis, with TC being the least common.

The boxplot analysis in Figure 1 reveals that the youngest patients were diagnosed with euthyroid Hashimoto thyroiditis (mean age 41.11 ± 13.71 years, median 39), TC (mean age 41.21 ± 14.45 years, median 41), and EDG (mean age 41.29 ± 13.07 years, median 40). The middle-aged patients had subacute thyroiditis (mean age 45.13 ± 13.7 years, median 44) and hyperthyroidism (mean age 45.15 ± 14.09 years, median 45). Older patients had ENG (mean age 47.86 ± 13.7 years, median 48) and hypothyroidism (mean age 47.9 ± 15.86 years, median 49). The oldest group was diagnosed with TNG (mean age 55.17 ± 13.7 years, median 58). Significant age differences ($P < 0.001$) were noted between patients with hypothyroidism and those diagnosed with euthyroid Hashimoto thyroiditis (mean age difference 6.79 years, 95% CI 3.81 to 9.77), hyperthyroidism (mean age difference 2.75 years, 95% CI 1.78 to 3.72), EDG (mean age difference 6.6 years, 95% CI 5.62-7.59), and TNG (mean age difference 7.28 years, 95% CI -9.77 to -4.78), but not for ENG (mean

Table 1: Distribution of thyroid pathology types by gender in the overall sample

Types of thyroid pathology	Gender		Total
	Women *n* (% of total)	Men *n* (% of total)	*n* (% of total)
Hypothyroidism	7,359 (35.24)	1083 (5.19)	8,442 (40.43)
Hashimoto thyroiditis	217 (1.0)	17 (0.12)	234 (1.12)
Euthyroid Nodular Goiter	5,342 (25.58)	651 (3.12)	5,993 (28.7)
Hyperthyroidism	2,308 (11.05)	569 (2.73)	2,877 (13.78)
Toxic Nodular Goiter	292 (1.4)	46 (0.22)	338 (1.62)
Subacute thyroiditis	145 (0.7)	32 (0.15)	177 (0.85)
Euthyroid Diffuse Goiter	2,490 (11.93)	290 (1.38)	2,780 (13.31)
Thyroid Carcinoma	29 (0.14)	10 (0.05)	39 (0.19)
Total	18,182 (87.08)	2,698 (12.92)	20,880 (100.0)

The results are presented with absolute (*n*) and relative values (%). Thyroid function was assessed based on TSH (0.4–4.0 μIU/mL), free thyroxine (fT4) (9.0–24.7 pmol/L), and thyroid peroxidase (TPO) antibodies (<35 mIU/mL) cut-off values. Toxic Nodular Goiter, Euthyroid Nodular Goiter, and Euthyroid Diffuse Goiter were assessed using thyroid ultrasound and thyroid function tests (TSH, fT4)

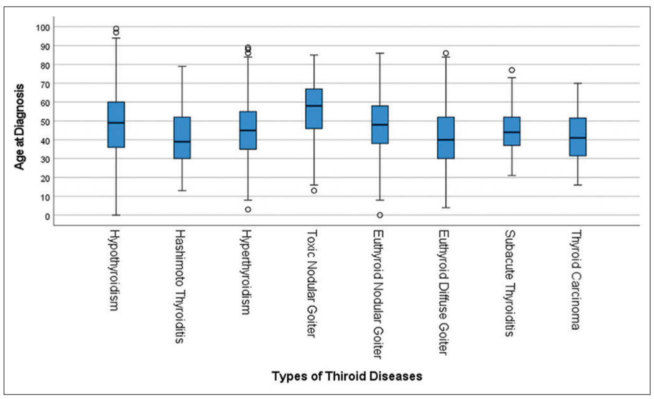

Figure 1: Box-plot analysis of the age at diagnosis across thyroid pathology types in the overall sample. The length of the box represents the 25th to 75th percentiles of the distribution of values. The horizontal black bar in the box indicates the median value. Vertical lines (whiskers) extend to the minimum and maximum values outside the 25th and 75th percentiles. An outlier data point is located outside the whiskers of the box plot

age difference 0.36 years, $P = 1.0$, 95% CI -0.72 to 0.8), subacute thyroiditis (mean age difference 2.77 years, $P = 0.215$, 95% CI −0.65 to 6.18), and TC (mean age difference 6.691 years, $P = 0.093$, 95% CI −0.53 to 13.91).

Figure 2 illustrates the annual incidence of TDs, which remained relatively stable until the 1999 iodine prophylaxis correction. Post-correction, the incidence inclined, peaking in 2010 (1,466 cases), coinciding with a rise in examinations (16,846 in 2009). Afterward, incidence declined, with a minor peak observed in 2019 (1,079 cases). Examination data, available from 2005 onwards, revealed a range from 11,422 in 2012 to 15,466 in 2011. The sharpest drop in TD incidence (461 cases) and exams (6,545) occurred in 2020 due to the COVID-19 pandemic, with examinations rebounding to 9,936 in 2021.

Before the 1999 iodine prophylaxis correction, the mean age at diagnosis was 40.03 ± 13.03 years (median 39, mode 41), with males accounting for 8.3% of cases. Post-correction, the mean age increased by 7.57 years to 47.54 ± 15.1 years (median 48, mode 54; $P < 0.001$, 95% CI −8.128 to −6.887), and male representation rose by 5.2% to 13.5% ($\chi^2 = 53.125$, $P < 0.001$, 95% CI 0.38–0.066).

As shown in Table 2, before the correction, two-thirds of the patients were diagnosed with ENG, hyperthyroidism, and EDG. Post-correction, hypothyroidism incidence significantly increased ($P < 0.001$), while the incidences of hyperthyroidism, EDG, TNG, TC, and subacute thyroiditis declined. The incidences of ENG ($P = 0.102$) and euthyroid Hashimoto's thyroiditis ($P = 0.089$) remained unchanged.

Table 3 reveals the annual TD incidence per 100,000 inhabitants in Region 1 for census years 1994, 2002, and 2021.[19] Despite the population decline, TD incidence rose significantly, with higher rates of hypothyroidism, euthyroid Hashimoto's thyroiditis, and subacute thyroiditis in 2021, alongside lower rates of EDG, hyperthyroidism, and TNG.

Discussion

This epidemiological study investigates the regional incidence of thyroid disorders over 37 years, focusing on the impact of the iodine prophylaxis correction in 1999. The observed female-to-male ratio of 6.7:1 is consistent with findings from the American Thyroid Association (ATA) and European meta-analyses.[4,5,20,21] Santin *et al*.[22] attribute this gender discrepancy to estrogen's impact on estrogen receptors α (ERα) and β (ERβ), with the ERα/Erβ ratio linked to the occurrence of ENG and TC.

The average patient age in the study was 47 years, aligning with the results of Hassan-Kadle *et al*.[1] and other studies showing increasing TD prevalence with age.[6,9] The higher average age at diagnosis in males, a pattern seldom reported, may reflect delayed healthcare-seeking behavior or biological factors. Further research is necessary to explore the gender-related age differences for screening, diagnosis, and treatment of TD in men.

Table 2: Comparison of types of thyroid diseases between Group 1 (1984–1999) and Group 2 (2000–2021)

Types of Thyroid Diseases	Group 1 (1984–1999) *n*=2,506 *n* (%)	Group 2 (2000 –2021) *n*=18,374 *n* (%)	Chi-squared (χ^2) test	*P*	Mean difference (95% Confidence interval – Lower, Upper)
Hypothyroidism	397 (15.84)	8045 (43.78)	713.76	<0.001	−27.94 (−29.54, −26.340)
Hashimoto thyroiditis	37 (1.48)	197 (1.01)	2.90	0.089	0.4 (−0.009, 0.90)
Euthyroid Nodular Goiter	684 (27.29)	5309 (28.89)	2.68	0.102	−1.6 (−3.46, 0.26)
Hyperthyroidism	621 (24.78)	2256 (12.28)	289.09	<0.001	12.5 (10.75, 14.26)
Toxic Nodular Goiter	78 (3.11)	260 (1.42)	38.84	<0.001	1.7 (1.0, 2.4)
Subacute thyroiditis	42 (1.68)	135 (0.73)	22.14.	<0.001	0.94 (0.42, 1.46)
Euthyroid Diffuse Goiter	625 (24.94)	2155 (11.73)	332.36	<0.001	13.21 (11.45, 14.97)
Thyroid carcinoma	22 (0.88)	17 (0.16)	68.81	<0.001	0.79 (0.42, 1.15)

The results are presented with absolute (*n*) and relative values (%). Thyroid function was assessed based on TSH (0.4–4.0 µIU/mL), free thyroxine (fT4) (9.0–24.7 pmol/L), and thyroid peroxidase (TPO) antibodies (<35 mIU/mL) cut-off values. Toxic Nodular Goiter, Euthyroid Nodular Goiter, and Euthyroid Diffuse Goiter were assessed using thyroid ultrasound and thyroid function tests (TSH, fT4)

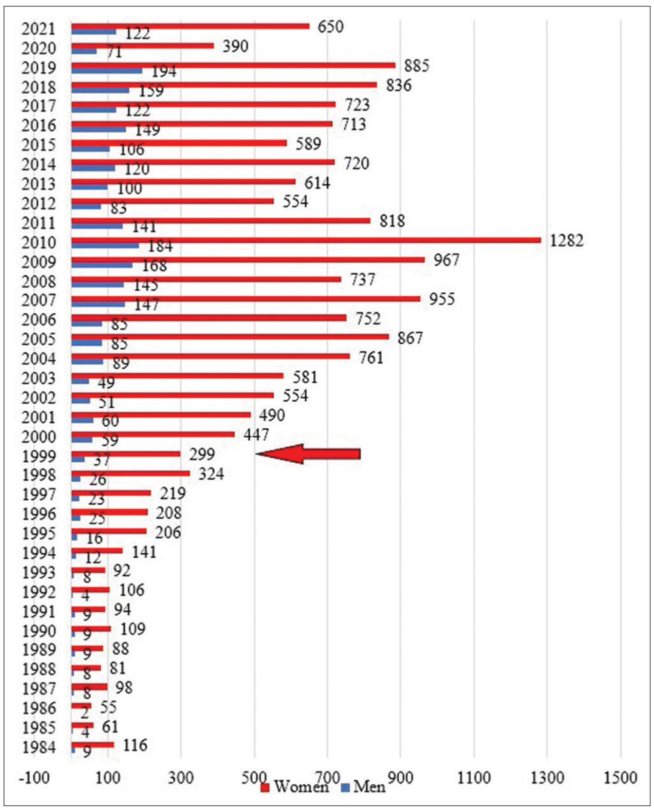

Figure 2: Gender representation and annual incidence of thyroid diseases in the overall sample. The results are presented with absolute values (*n*)

Hypothyroidism was the most prevalent disorder (40.43%), reflecting global trends,[6,9] followed by ENG (28.7%), matching ATA expectations.[4] Hyperthyroidism and EDG each constituted 13% of cases, indicating typical prevalence patterns. Supporting data from the NHANES III survey reported a 4.6% prevalence of hypothyroidism and 1.3% for hyperthyroidism in the USA (1988-1994).[23] A 2014 European meta-analysis found a 3.82% prevalence of thyroid dysfunction, with hypothyroidism at 3.05% and hyperthyroidism at 0.75%.[20] A 2019 European meta-analysis revealed a high prevalence of undiagnosed subclinical hypothyroidism at 4.11%.[21] TNG, euthyroid Hashimoto's thyroiditis, subacute thyroiditis, and TC were rare (3.78% combined), consistent with their global low prevalence.[6] These findings underscore the need for improved screening to enable the early detection of subclinical hypothyroidism and prevent long-term health consequences.

The study revealed that younger patients, around 40 years old, were more likely to be diagnosed with euthyroid Hashimoto thyroiditis, TC, or EDG, while TNG was more prevalent in those around 55. Patients suffering from hyperthyroidism were diagnosed at a mean age of 45, significantly younger compared to patients with hypothyroidism and ENG (mean age of 47), consistent with Taylor *et al*.[6] These age differences underscore the importance of age-specific screening and management strategies, warranting further investigation into genetic, hormonal, and environmental factors influencing TD development.

Iodine deficiency has been linked to hypothyroidism, diffuse and nodular goiter, and follicular TC. Lisco *et al*.[24] emphasize the importance of iodine prophylaxis, particularly salt iodization, in reducing iodine deficiency disorders in endemic areas. The 1999 iodine prophylaxis correction targeted mild to moderate deficiency and significantly influenced TD patterns.[15,25] Before the correction, low TD incidence likely mirrored initial diagnoses at the national tertiary center and lost records. Post-correction, incidence increased, peaking in 2010, reflecting adjusted iodine intake and increased examinations, aligning with findings by Shan *et al*. in China.[26] Afterward, incidence declined, with a notable rise in 2019. In 2020, COVID-19 restrictions led to a sharp decrease in new cases and examinations. The improvement in iodine status led to a higher proportion of male patients and an increase in the median age at diagnosis from 39 to 48 years. These findings could not be directly compared with other studies due to a lack of similar data in the existing literature. Further research into environmental and lifestyle factors is needed.

The iodine prophylaxis correction notably altered the TD spectrum. Pre-correction, two-thirds of patients had ENG, hyperthyroidism, and EDG, aligning with the findings

Table 3: Incidence of thyroid diseases per 100,000 inhabitants in Region 1 for census years

Census years	1994		2002		2021	
Inhabitants in the Region 1	242,614		238,136		210,431	
	n	I*	*n*	I*	*n*	I*
Total number of thyroid patients per year	153	63.06	605	254.06	772	366.87
Hypothyroidism	15	6.18	138	57.95	449	213.37
Hashimoto thyroiditis	4	1.64	0	0	45	21.38
Euthyroid Nodular Goiter	44	18.14	202	84.83	187	88.87
Hyperthyroidism	46	18.96	110	46.19	73	34.69
Toxic Nodular Goiter	2	0.82	17	7.14	4	1.90
Subacute Thyroiditis	4	1.64	4	1.68	8	3.80
Euthyroid Diffuse Goiter	37	15.25	132	55.43	6	2.85
Thyroid Carcinoma	1	0.41	2	0.84	0	0

The results are presented with absolute values (*n*). *Incidence per 100,000 inhabitants. Thyroid function was assessed based on TSH (0.4–4.0 µIU/mL), free thyroxine (fT4) (9.0–24.7 pmol/L)), and thyroid peroxidase (TPO) antibodies (<35 mIU/mL) cut-off values. Thyroid ultrasound and thyroid function tests (TSH, fT4) were used to assess Toxic Nodular Goiter, Euthyroid Nodular Goiter, and Euthyroid Diffuse Goiter

by Loparska *et al*.[17] Post-correction, hypothyroidism incidence rose sharply, affecting nearly half of the patients. Hyperthyroidism, EDG, and TNG declined, consistent with Lisco *et al*.[24] Switzerland was the first to introduce universal iodine fortification, proving its effectiveness in preventing thyroid enlargement, goiter, and other iodine deficiency disorders (IDD). Both Switzerland and Austria observed a temporary increase in hyperthyroidism following implementation. Similarly, the Danish national study, DanThyr, reported an initial spike in hyperthyroidism incidence after iodine fortification, which later declined below pre-fortification levels, whereas TSH levels, thyroid autoimmunity prevalence, hypothyroidism incidence, and multinodularity increased.[27] In Croatia, Strikić Đula *et al*.[9] reported increased hypothyroidism and stable hyperthyroidism post-1996 iodine prophylaxis. They identified a high prevalence of undiagnosed thyroid disorders, including 92.6% of subclinical and 93.9% of clinical hypothyroidism, and 83% of subclinical and 71.4% of clinical hyperthyroidism. Similarly, Shan *et al*.[26] observed a rise in thyroid disorders in China post-correction, particularly clinical and subclinical hypothyroidism, positive thyroid antibodies, and nodular goiter. However, clinical and subclinical hyperthyroidism and Graves' disease remained unchanged, while diffuse goiter declined. In India, following the correction of iodine prophylaxis, Unnikrishnan *et al*.[28] reported a 3.9% prevalence of hypothyroidism among adults, with subclinical hypothyroidism at 9.4%. Subclinical and overt hyperthyroidism were observed in 1.6% and 1.3% of individuals, respectively, while the prevalence of goiter did not show a significant decline. All these national studies associated shifts in the TD spectrum with iodine prophylaxis correction, accentuating its relevance in eliminating IDD.

Euthyroid Hashimoto's thyroiditis had no significant change, likely due to limited data confirming AITD, unlike studies on TD prevalence following mandatory iodine fortification in China and Denmark.[11,26,27] Following the iodine prophylaxis correction, TC incidence decreased, contrasting with trends observed in the USA, where TC cases rose from 4.9 per 100,000 in 1975 to 14.3 per 100,000 in 2009.[4] These findings highlight iodine prophylaxis's role in TD trends and the need for further research and monitoring.

The incidence of TD in Region 1 rose from 63.07 per 100,000 in 1994 to 367 per 100,000 in 2021, despite a declining population. Hypothyroidism increased significantly, from 57.95 per 100,000 in 2002 to 213.37 per 100,000 in 2021, reflecting improved detection, iodine prophylaxis, and an aging population, aligning with the 2019 European meta-analysis (226.2 per 100,000).[21] Hyperthyroidism peaked in 2002 (46.19 per 100,000) but declined to 34.69 per 100,000 by 2021, mirroring the findings of the DanThyr study.[27] Lower hyperthyroidism rates compared to the 2019 European meta-analysis (51 per 100,000) may indicate underdiagnosis of subclinical forms.[21] Hashimoto thyroiditis emerged by 2021, driven by greater awareness, advanced tests, and adequate iodine intake, consistent with studies linking higher iodine levels to AITD and hypothyroidism.[11,26,27] ENG increased from 1994 to 2002, stabilizing by 2021, contrary to findings by Tang Møllehave *et al*.[27] TNG and EDG showed a temporary rise in 2002 but declined by 2021, reflecting reduced iodine deficiency, as noted by Censi *et al*.[29] Subacute thyroiditis peaked in 2021, potentially influenced by the COVID-19 pandemic. TC remained rare, likely due to referrals to a national tertiary center for fine-needle aspiration biopsy. Makazlieva *et al*.[30] reported a slight increase in TC incidence from 1999 to 2010, mainly papillary TC, while more aggressive types like follicular and anaplastic TC declined, attributed to the iodine prophylaxis correction. Similarly, Unnikrishnan *et al*.,[28] using data from the Mumbai Cancer Registry, reported TC incidence rates of approximately 1 per 100,000 in males and 1.8 per 100,000 in females. Papillary TC was the most common subtype, followed by follicular carcinoma. These trends underscore the beneficial impact of iodine prophylaxis on thyroid health and the significance of continued research.

Strengths and limitations of the study

The study's primary strength is its extensive 37-year timeline, offering valuable insights into thyroid pathology trends within the region. Unique variations in thyroid disorders influenced by local environmental and demographic factors provide region-specific public health recommendations. The analysis of 20,880 medical records enhances the study's relevance and reliability.

Limitations include biases from its retrospective design, reliance on available medical records, a smaller pre-correction sample size due to record removals after patient mortality, the absence of electronic data, and the initial diagnosis of patients at the tertiary center. The decline in 2020 cases likely reflects COVID-19-related restrictions. Missing data on yearly examinations before 2005 and the precise date of birth limit long-term trends and age-related analyses. The lack of data regarding the autoimmune origin of hypothyroidism affects AITD representation. Lastly, the regional findings may not be generalizable to areas with different iodine fortification histories or healthcare systems.

Implications for public health and practice

Continued monitoring of TD trends post-iodine prophylaxis correction is needed. Targeted screening for age and gender risk groups and early detection is essential. Public health efforts should focus on raising awareness about dietary factors, goitrogenic substances, and salt intake while prioritizing mandatory iodine prophylaxis to maintain optimal thyroid health. Iodine fortification is a cost-effective intervention with significant economic benefits, reducing iodine deficiency disorders (IDD), lowering healthcare costs, and enhancing public health. It supports cognitive development, improves workforce productivity, and contributes to economic growth. However, iodine fortification increased the incidence of some TD, raising therapy needs, surgical procedures, and healthcare costs. These observations align with findings by Tang Møllehave *et al*.,[27] who reported an increase in Danish TD treatment costs, mainly due to more thyroid hormone therapies and a slight rise in expensive surgeries. However, the benefits of iodization outweigh the drawbacks. Continuous monitoring of iodine status is essential to optimize the benefits of iodine prophylaxis, a strategic investment in public health and national development.

Many international organizations, including Thyroid Federation International (TFI), help improve global thyroid health. Through public education campaigns and collaborations with healthcare professionals and governments, TFI promotes the benefits of adequate iodine intake and universal salt iodization. It actively monitors iodine levels worldwide and evaluates the effectiveness of iodine fortification programs, supporting data collection to identify iodine deficiency regions and implement targeted interventions. Moreover, TFI contributes to research through its involvement in EUthyroid1 and EUthyroid2 projects aimed at eliminating iodine deficiency and preventing IDD across Europe and beyond. Their efforts help integrate iodine-related strategies into national health policies, reinforcing the global commitment to thyroid health.

Recommendations for future research

Additional research is needed to understand the mechanisms linking iodine prophylaxis to TD changes. Collaborative studies could investigate genetic, environmental, and dietary factors affecting regional variations. Clinical research should emphasize long-term monitoring, early detection of subclinical thyroid dysfunction, and targeted prevention and management strategies by age and gender.

Conclusion

Hypothyroidism and ENG were predominant thyroid pathologies in the area. The correction of iodine prophylaxis raised the overall TD incidence, age at diagnosis, male representation, and hypothyroidism while reducing hyperthyroidism, EDG, and TNG. ENG remained stable, warranting further investigation. These findings underscore the significant effect of iodine intake on TD incidence and spectrum. Continued monitoring and research, including other environmental factors, are essential for understanding these trends and improving public health strategies for TD management.

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Author contributions

Contributor 1; guarantor – Todorovska Liljana: conceptualization, methodology, design, data collection, definition of intellectual content, literature search, data acquisition, data analysis, manuscript preparation, and manuscript editing.

Contributor 2 – Avramovski Petar: statistical analysis, manuscript preparation, manuscript editing, and review.

Contributor 3 – Avramovska Maja: conceptualization, methodology, data collection, definition of intellectual content, literature search, and manuscript preparation.

Contributor 4 – Todorovski Jovan: conceptualization, methodology, data collection, data analysis, statistical analysis, and manuscript preparation.

Contributor 5 – Vaskova Olivija: conceptualization, methodology, manuscript editing, and manuscript review.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence

None.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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